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REPORT

BIOASSAY OF TOXAPHENE FOR POSSIBLE CARCINOGENICITY

Carcinogenesis technical report series

Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

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V. DISCUSSION

Mean body weights attained by low- and high-dose female rats and high-dose male mice were lower than those of matched controls, but weights of other dosed groups were essentially unaffected by the toxaphene. Other clinical signs of toxicity included generalized body tremors in high-dose male and female rats at week 53, after which the concentrations of toxaphene were reduced. Later, leg paralysis, ataxia, epistaxis, hematuria, and vaginal bleeding were observed in a few animals, predominantly in the dosed groups. Abdominal distention, diarrhea, dyspnea, and rough hair coats were observed predominantly in the dosed groups of both rats and mice; the abdominal distention was noted particularly among the high-dose male mice. Several high-dose male mice died during later weeks of the study, and the survival rates showed a significant dose-related trend in male mice. High-dose female mice had a significant decrease in survival. Sufficient numbers of both rats and mice were at risk for the development of late-appearing tumors.

In the male rats, the incidence of follicular-cell carcinomas or adenomas of the thyroid was dose related ($P = 0.007$) using the pooled controls (matched controls 1/7, pooled controls 2/44,

low-dose 7/41, high-dose 9/35). In the females, the incidence of follicular-cell adenomas of the thyroid was dose-related using either the matched (P = 0.022) or pooled (P = 0.008) controls (matched controls 0/6, pooled controls 1/46, low-dose 1/43, high-dose 7/42). Direct comparisons of dosed and pooled-control groups showed significantly increased incidences of the follicular-cell carcinomas or adenomas in the high-dose males (P = 0.008) and of the follicular-cell adenomas in the high-dose females (P = 0.021). Two follicular-cell tumors in the high-dose males were carcinomas; all other follicular-cell tumors in the rats were adenomas.

In the female rats, the incidence of tumors of the pituitary (adenomas, chromophobe adenomas, and chromophobe carcinomas) was dose related using either matched (P = 0.046) or pooled (P = 0.012) controls, and, in a direct comparison, the incidence of pituitary tumors in the high-dose group was significantly higher (P = 0.013) than that in the pooled-control group (matched controls 3/8, pooled controls 17/51, low-dose 15/41, high-dose 23/39). One pituitary tumor, in a high-dose female, was a carcinoma; all other pituitary tumors in the rats were adenomas. The historical-control data obtained to date on 20 similar studies at this laboratory show an incidence of pituitary tumors of 58/185 (31.4 %), although there are incidences as high as 6/10

(60%), 5/10 (50%), 3/6 (50%), and 4/9 (44%). Considering these high spontaneous incidences observed in control groups, the conclusion cannot be made that the tumors in this study are associated with the administration of the test chemical.

In the mice, the incidence of hepatocellular carcinomas was dose related (P less than 0.001) for both males (matched controls 0/10, pooled controls 4/48, low-dose 34/49, high-dose 45/46) and females (matched controls 0/9, pooled controls 0/48, low-dose 5/49, high-dose 34/49), using either matched or pooled controls. Direct comparisons showed that the incidences of hepatocellular carcinomas in low- and high-dose male mice and high-dose female mice were all significantly higher (P less than 0.001) than those in the respective matched or pooled controls. Statistical significance was maintained when the incidence of hepatocellular carcinomas was combined with that of neoplastic nodules of the liver.

Both the FDA in 1949 and Kettering Laboratories in 1952 (Lehman, 1965) conducted 2-year feeding studies of toxaphene in rats (strain not specified). Concentrations of toxaphene used in the two investigations were 25, 100, 400, and 1,600 ppm and 10, 100, 1,000, and 1,500 ppm, respectively. Histologic changes in the liver were noted in rats given more than 25 ppm in the FDA study

and more than 100 ppm in the Kettering study, but no increase in the incidence of tumors was noted. Doses used in the present study fall within these ranges. Sherman rats fed 50 or 200 ppm toxaphene in the diet for 9 months did not show clinical signs, but on histopathologic examination, mild liver changes were found in some of the dosed animals (Ortega et al., 1957). In other studies, hybrid mice were administered the related chemical, Strobane®, at 4.64 mg/kg by stomach tube for 3 weeks, then at a concentration of 11 ppm in the diet for 75 weeks (Innes et al., 1969). A significantly elevated incidence of hepatomas was reported in male C57BL/6 x C3H/AnF hybrid mice and of lymphomas in male C57BL/6 x AKR hybrid mice.

It is concluded that under the conditions of this bioassay, toxaphene was carcinogenic in male and female B6C3F1 mice, causing increased incidences of hepatocellular carcinomas. The test results also suggest carcinogenicity of toxaphene for the thyroid of male and female Osborne-Mendel rats.